REMARKS

Claims 1-27 and 30-36 are pending in the above-identified application. New claim 39 has been added. Support for new claim 39 can be found throughout the application as filed and at, for example, page 5, lines 4-19. Applicant has reviewed the Advisory Action mailed September 29, 2004, and respectfully traverses all grounds for rejecting the application for the reasons that follow.

Rejections Under 35 U.S.C. § 112

Claims 1-27 and 30-36 remain rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement allegedly because it would be unpredictable to practice the invention as claimed. The Office maintains that the only contemplated use for the targeting construct, vector and cell is to make the claimed mouse. However, since the mouse is not enabled, the only contemplated use for the construct, vector and cell also is not enabled. The Office further maintains that Lem "clearly indicates" that disruption of both alleles of the rhodopsin gene results in the failure of the ROS to form in the transgenic animals. Ryan et al. is again relied upon allegedly because targeted homologous recombination also has a positional effect in view of the teachings of Lem that functional disruption of the rhospdin gene results in the failure of the ROS to develop in the transgenic mouse. Holschneider also is again relied upon allegedly because knocking out of genes can result in unexpected phenotypes. The Office further acknowledges that the claimed invention has utility.

As previously acknowledged, the law is clear with respect to undue experimentation. Routine experimentation, even if it is time consuming, does not constitute undue experimentation. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998).

Applicant maintains that Ryan et al. does not state or suggest that expression is unpredictable. Rather, Ryan et al. states that transgenic expression by random genome insertion is associated with certain disadvantages such as "differences in transgene copy number and position of integration in the genome" and "differences in baseline phenotypes" reported in different genetic backgrounds (Office Action at page 5, *quoting* Ryan et al.). Further, the

reported disadvantages in Ryan et al. are stated in context of constructing a animal model that "perfectly emulate[s] a gene at its normal location in the genome" (Office Action at page 5, *quoting* Ryan et al.). Such descriptions do not amount to undo experimentation for making and using the invention as claimed.

For example, Applicant maintains that production of an animal model that perfectly emulates a gene at it's normal locus differs from the purpose of the claimed invention. Additionally, the constructs, cells and mice of the claimed invention place the transgene in a normal locus for rhodopsin. Therefore, the claimed flanking sequences avoid the deficiencies described by Ryan et al. and render its description inapplicable as support for unpredictability. In contranst, any description in Ryan et al. regarding unpredictability is associated with random transgenic expression, which is distinct in both the method of insertion and in the obtained results. Accordingly, the claimed cell and mouse are not fraught with disadvantages such as variable transgene copy number and position of integration observed using random insertion methods which led to variation in expression levels described by Ryan et al.

Additionally, the application teaches and the claims are directed to a gene targeting construct, a cell and a mouse produced from the claimed construct that results in the homologous recombination or site specific recombination of the transgene at the rhodopsin gene locus in such a manner that expression will occur. The claimed constructs, vectors and mouse are enabled for this taught utility. Nevertheless, Applicants have added new claim 39 which expressly recites that sufficient expression results from said transgene to produce an encoded polypeptide. Accordingly, Applicant has enabled any mouse resulting from the claimed constructs and vectors and also has specifically claimed a mouse that results in expression of a transgene encoded polypeptide.

Applicant maintains that Lem et al. expressly describe the normal development of retinas in mice in a rhodopsin-null mouse, when Lem et al. state:

> Retinas in mice lacking both opsin alleles initially developed normally.

Abstract at page 736 (emphasis added). Such descriptions are sufficient to preclude any assertion of undue experimentation of the claimed invention.

Further, and as pointed out previously, Lem et al. expressly describe a solution to overcome any lack of normal development of retinas in rhodopsin knock-out mice. In this regard, Lem et al. describe that any later stage retinal development problems can be circumvented by constructing a single rhodopsin gene knock-out instead of both alleles. The claimed mouse is directed to having a functional disruption of one or both endogenous rhodopsin gene alleles. Therefore, any experimentation required to produce the claimed mouse cannot be considered undue in light of this claimed element, the teachings in the application, as well as the solutions proposed by the cited reference.

Applicant maintains that Holschneider et al. is nonanalogous to the claimed invention because the application describes and claims the construction of a transgene encoding polypeptide having a ROS target signal flanked by sequences for homologous recombination that is operable association with a rod-specific regulatory signal. Holschneider et al. are concerned with observing changes in phenotype. Because Applicant claims an operable association, the claims exclude those embodiments that fail to produce expressed transgenic polypeptide in the ROS. Accordingly, Holschneider et al. and the assertion that a phenotype requiring transgene expression fails to provide an adequate basis for lack of predictability of the claimed invention.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP

David A. Gay
Registration No. 39,200

4370 La Jolla Village Drive, Suite 700
San Diego, CA 92122
Phone: 858.535.9001 DAG:jrl
Facsimile: 858.597.1585
Date: March 23, 2005

Please recognize our Customer No. 41552 as our correspondence address.